PATENT
Docket No. 395/35

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor	:	Gerard M. HOUSEY
Serial No.	:	09/510,562
Filing Date	:	February 22, 2000
For:	:	METHOD FOR SCREENING FOR PROTEIN INHIBITORS AND ACTIVATORS
Examiner	:	Saunders, David A.
Art Unit	:	1643

Assistant Commissioner for Patents
Washington D.C. 20231

SECOND PRELIMINARY AMENDMENT

Sir:

Prior to examination, kindly amend the above-identified application as follows:

IN THE CLAIMS:

Please cancel Claims 31 and 32 without prejudice.

Please add the following claims:

33. A method of determining whether a chemical agent that directly interacts with an enzyme is an inhibitor or activator of that enzyme whose production by a cell evokes a responsive change in a phenotypic characteristic of the cell, other than the level of said enzyme in said cell per se, which comprises:

(a) providing a first mammalian cell line which produces said enzyme and exhibits said phenotypic response to the enzyme;

(b) providing a second mammalian cell line which produces the enzyme at a lower level than the first cell line, or does not produce the enzyme at all, and which exhibits said phenotypic response to the enzyme to a lesser degree or not at all;

(c) incubating the chemical agent with the first and second cell lines; and

(d) comparing the phenotypic response of the first cell line to the chemical agent with the phenotypic response of the second cell line to the chemical agent.

34. The method of Claim 33 wherein said first cell line is obtained by introducing a gene encoding said enzyme into a host cell, said gene being under the control of a promoter functional in the host cell, whereby said gene is expressed.

35. The method of Claim 34 wherein the gene is introduced into the host cell by means of a first genetic vector into which the gene has been inserted, and said second cell line is obtained by introducing into a similar host cell a second genetic vector essentially identical to the first genetic vector except that it does not bear said gene insert.

36. The method of any one of Claims 33-35 wherein said chemical agent is a suspected inhibitor of the biological activity of said enzyme.

37. The method of any one of Claims 33-35 wherein said chemical agent is a suspected activator of the biological activity of said enzyme.

38. The method of any one of Claims 33-35 wherein the phenotypic response of said first cell line upon incubation with said chemical agent is a graded cellular response.

39. A method of determining whether a chemical agent that directly interacts with a protein is an inhibitor or activator of that protein whose production by a cell evokes a responsive change in a phenotypic characteristic of the cell, other than the level of said protein in said cell per se, which comprises:

(a) providing a first mammalian cell line which produces said protein and exhibits said phenotypic response to the biological activity of the protein;

(b) providing a second mammalian cell line which produces the protein at a lower level than the first cell line, or does not produce the protein at all, and which exhibits said phenotypic response to the biological activity of said protein to a lesser degree or not at all;

(c) incubating the chemical agent with the first and second cell lines, wherein said chemical agent is suspected of being an inhibitor or activator of the biological activity of the protein; and

(d) comparing the phenotypic response of the first cell line to the chemical agent with the phenotypic response of the second cell line to the chemical agent.

40. The method of Claim 39 wherein said first cell line is obtained by introducing a gene encoding said protein into a host cell, said gene being under the control of a promoter functional in the host cell, whereby said gene is expressed.

41. The method of Claim 40 wherein the gene is introduced into the host cell by means of a first genetic vector into which the gene has been inserted, and said second cell line is obtained by introducing into a similar host cell a second genetic vector essentially identical to the first genetic vector except that it does not bear said gene insert.

42. The method of any one of Claims 39-41 wherein the phenotypic response of said first cell line upon incubation with said chemical agent is a graded cellular response.

43. A method of determining whether a chemical agent that directly interacts with an enzyme is an inhibitor or activator of that enzyme which comprises:

(a) providing a mammalian test cell which overproduces a selected enzyme relative to a mammalian control cell which produces said enzyme at a lower level or essentially does not produce the enzyme, and wherein production of said enzyme in said test cell evokes a

responsive change in a phenotypic characteristic of said test cell, other than the level of said enzyme in said test cell per se, which is comparatively greater than in said control cell;

(b) treating said test cell containing the overproduced selected enzyme with said chemical agent; and

(c) examining the treated test cell to determine whether it exhibits a change in said phenotypic characteristic in response to said chemical agent.

44. The method of Claim 43 wherein said test cell is obtained by introducing a gene encoding said enzyme into a host cell, said gene being under the control of a promoter functional in the host cell, whereby said gene is expressed.

45. The method of Claim 44 wherein the gene is introduced into said host cell by means of a first genetic vector into which the gene has been inserted, and said control cell is obtained by introducing into a similar host cell a second genetic vector essentially identical to the first genetic vector except that it does not bear said gene insert.

46. The method of Claim 43 wherein examination for a change in the phenotypic characteristic in response to said chemical agent includes comparing the response of the treated cell to the response of a comparable untreated test cell.

47. The method of Claim 43 wherein examination includes comparing the phenotypic response of the treated test cell to that of a comparably treated test cell which does not overproduce the selected enzyme.

48. The method of Claim 43 wherein examination includes comparing the phenotypic response of the first test cell in the presence of said chemical agent with the phenotypic response of the second test cell in the presence of a known inhibitor or activator of the enzyme.

49. The method of any one of Claims 43-48 wherein said chemical agent is a suspected inhibitor of the biological activity of said enzyme.

50. The method of any one of Claims 43-48 wherein said chemical agent is a suspected activator of the biological activity of said enzyme.

51. The method of any one of Claims 43-48 wherein said change in said phenotypic characteristic in response to said chemical agent is a graded cellular response.

52. A method of determining whether a chemical agent that directly interacts with a protein is an inhibitor or activator of that protein which comprises:

(a) providing a mammalian test cell which overproduces a selected protein relative to a mammalian control cell which produces said protein at a lower level or essentially does not produce the protein, and wherein production of said protein in said test cell evokes a responsive change in a phenotypic characteristic of said test cell, other than the level of said protein in said test cell per se, which is comparatively greater than in said control cell;

(b) treating said test cell containing the overproduced selected protein with said chemical agent, wherein said chemical agent is suspected of being an inhibitor or activator of the biological activity of said protein; and

(c) examining the treated test cell to determine whether it exhibits a change in said phenotypic characteristic in response to said chemical agent.

53. The method of Claim 52 wherein said test cell is obtained by introducing a gene encoding said protein into a host cell, said gene being under the control of a promoter functional in the host cell, whereby said gene is expressed.

54. The method of Claim 53 wherein the gene is introduced into said host cell by means of a first genetic vector into which the gene has been inserted, and said control cell is

obtained by introducing into a similar host cell a second genetic vector essentially identical to the first genetic vector except that it does not bear said gene insert.

55. The method of Claim 52 wherein examination for a change in the phenotypic characteristic in response to said chemical agent includes comparing the response of the treated cell to the response of a comparable untreated test cell.

56. The method of Claim 52 wherein examination includes comparing the phenotypic response of the treated test cell to that of a comparably treated test cell which does not overproduce the selected protein.

57. The method of Claim 52 wherein examination includes comparing the phenotypic response of the first test cell in the presence of said chemical agent with the phenotypic response of the second test cell in the presence of a known inhibitor or activator of the protein.

58. The method of any one of Claims 52-57 wherein said change in said phenotypic characteristic in response to said chemical agent is a graded cellular response.

REMARKS

The courtesy of the Examiner in granting Applicant and his representatives a pre-examination interview is gratefully acknowledged. As indicated at that interview, Applicant hereby submits new Claims 33-58 which are based on claims in Applicant's issued patents, U.S. Patent Nos. 4,980,281 and 5,688,655 (hereinafter the '281 patent and the '655 patent, respectively). Accordingly, Applicant encloses a terminal disclaimer with respect to the '281 and '655 patents.

As the Examiner is aware, some, **but not all**, of the claims in the '281 and '655 patents were originally declared by the PTO to interfere with the single claim in U.S. Serial

No. 08/953,550 of Berman *et al.* (hereafter "Berman") as set out in Interference No. 104,347.[1] To expedite prosecution, the claims presented in this application are based **only** on claims in the '281 and '655 patents which were determined **not** to correspond to the count of the interference. *See*, Notice Declaring Interference, Page 32, indicating that Claims 2, 4-14, 19-20 and 24 of the '281 patent and Claims 6, 8 and 14 of the '655 patent do **not** correspond to the count (copy enclosed) and the Interference Initial Memorandum with Attachment, also so-indicating (copy enclosed).

More particularly, in the newly presented claims, one group is directed to a method of determining whether a chemical agent that directly interacts with an enzyme is an inhibitor or activator of that protein as set forth in independent Claims 33 and 43 and the claims dependent thereon. The other group is directed to a method of determining whether a chemical agent, suspected of being an inhibitor or activator of the biological activity of a protein, that directly interacts with that protein is an inhibitor or activator of that protein as set forth in independent Claims 39 and 52 and the claims dependent thereon.

Claim 33 is based on Claim 8 of the '281 patent, and Claim 43 is based on Claim 8 of the '655 patent. Claim 39 is based on Claims 13 and 14 of the '281 patent, and Claim 52 is based on Claim 1 of the '655 patent and Claims 13 and 14 of the '281 patent. Each of the independent claims hereof includes all the elements of the claims on which they are based, a further limitation that the cells or cell lines used in the method are of *mammalian* origin, and

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[1]At present, Berman has no claim corresponding to the count, having been unable to satisfy the requirements of 35 U.S.C. § 135(b) for a timely claim directed to substantially the same subject matter as any of Applicant's patent claims. Berman's unpatentable claim was directed to a method of identifying inhibitors of HIV gp120. Berman is now attempting to add a claim directed to an antibody and have that claim designated as corresponding to a count made up of Claims 1 and 22 of the '281 patent, Claim 5 of the '464 patent, and Claim 1 of the '655 patent.

other recitations made to avoid assertions by third-parties attempting to broaden the scope of the claims. To assist in considering the new claims, a copy of Claims 33 and 43 has been included with the additions relative to Claim 1 of the '281 patent and Claim 1 of the '655 patent, respectively, shown in bold. A similarly marked copy of Claims 39 and 52 has also been included. *See,* Appendix 1.

Accordingly, support for the subject matter of Claims 33-58 is found, *inter alia*, in the present application and in the earliest priority application, U.S. Serial No. 07/154,206, which specification is identical to the '281 patent, as set forth in the tables below. The independent claims are presented first. No new matter has been presented.

Claim No. or Claim Element**	Application	'281 patent
33	Claim 1; Page 8, Lines 22-31; Claim 8; Page 1, Lines 12-14; Page 4, Lines 20-24	Claim 1; Col. 4, Lines 41-50; Claim 8; Col. 1, Lines 7-10; Col. 2, Lines 46-50
39	Claims 1, 13 & 14; Page 8, Lines 22-31; Page 38, line 33 to Page 39, line 6	Claims 1, 13 & 14; Col. 4, Lines 41-50; Col. 18, lines 9-17
43	Page 8, Lines 22-31; Claim 8; Page 1, Lines 12-14; Page 4, Lines 20-24	Col. 4, Lines 41-50; Claim 8; Col. 1, Lines 7-10; Col. 2, Lines 46-50 (see also Claims 1 and 8 of the '655 patent)
52	Page 8, Lines 22-31; Claims 13 & 14; Page 38, line 33 to Page 39, line 6	Col. 4, Lines 41-50; Claims 13 & 14 (see also Claim 1 of the '655 patent); Col. 18, lines 9-17
chemical agent	Page 13, Lines 3-7; Page 39, Lines 21-26	Col. 6, Lines 29-33; Col. 18, Lines 30-36
agent directly interacts with a protein/enzyme	Page 13, Lines 3-7; Page 39, Lines 21-26; Page 1, Lines 15-19; Page 5, Lines 14-19; Page 15, Lines 20-21	Col. 6, Lines 29-33; Col. 18, Lines 30-36; Col. 1, lines 10-15; Col. 3, Lines 5-10; Col. 7, Lines 41-42

Claim No. or Claim Element**	Application	'281 patent
phenotypic characteristic of a cell	Page 8, Line 33-Page 9, Line 1	Col. 4, Lines 51-54
mammalian	Page 39, Lines 21-26	Col. 18, Lines 30-36
34, 40, 44, 53	Claim 15	Claim 15
35, 41, 45, 54	Claim 16	Claim 16
36, 49	Claim 13	Claim 13
37, 50	Claim 14	Claim 14
38, 42, 51, 58	Page 4, Lines 13-16 and Line 35-Page 5, line 2; Page 12, Lines 22-28	Col. 2, Lines 40-43 and 60-63; Col. 6, Lines 14-20
46, 55	Page 8, Lines 29-31; Page 21, Lines 6-10	Col. 4, Lines 48-50; Col. 9, Lines 31-36 (see also Claim 2 of the '655 patent)
47, 56	Page 8, Lines 29-31; Page 21, Lines 6-10	Col. 4, Lines 48-50; Col. 9, Lines 31-36 (see also Claim 3 of the '655 patent)
48, 57	Page 8, Lines 29-31; Page 22, Lines 17-22	Col. 10, Lines 5-20 (see also Claim 5 of the '655 patent)

**These terms appear in independent Claims 33, 39, 43, and 52. The recited support applies for the terms as they appear those claims.

As discussed at the interview, Applicant encloses a copy of the decision in the opposition to Applicant's corresponding European Patent No. 0 403 506, where applicant prevailed over three oppositions, *see, e.g.*, Page 11, Paragraph 17, Line 6 and Page 21, Paragraph 49.

In view of the foregoing amendments and remarks, it is firmly believed that Claims 33-58 are in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

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Dated: July 11, 2000

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Appendix A

33. A method of determining whether a **chemical agent** [substance] **that directly interacts with an enzyme** [protein] is an inhibitor or activator of **that enzyme** [a protein] whose production by a cell evokes a responsive change in a phenotypic characteristic **of the cell**, other than the level of said **enzyme** [protein] in said cell per se, which comprises:

(a) providing a first **mammalian** cell line which produces said **enzyme** [protein] and exhibits said phenotypic response to the **enzyme** [protein];

(b) providing a second **mammalian** cell line which produces the **enzyme** [protein] at a lower level than the first cell line, or does not produce the **enzyme** [protein] at all, and which exhibits said phenotypic response to the **enzyme** [protein] to a lesser degree or not at all;

(c) incubating the **chemical agent** [substance] with the first and second cell lines; and

(d) comparing the phenotypic response of the first cell line to the **chemical agent** [substance] with the phenotypic response of the second cell line to the **chemical agent** [substance].

39. A method of determining whether a **chemical agent** [substance] **that directly interacts with a protein** is an inhibitor or activator of **that** [a] protein whose production by a cell evokes a responsive change in a phenotypic characteristic **of the cell**, other than the level of said protein in said cell per se, which comprises:

(a) providing a first **mammalian** cell line which produces said protein and exhibits said phenotypic response to **the biological activity of** the protein;

(b) providing a second **mammalian** cell line which produces the protein at a lower level than the first cell line, or does not produce the protein at all, and which exhibits said phenotypic response **to the biological activity of** the protein to a lesser degree or not at all;

(c) incubating the **chemical agent** [substance] with the first and second cell lines, **wherein said chemical agent is suspected of being an inhibitor or activator of the biological activity of said protein**; and,

(d) comparing the phenotypic response of the first cell line to the **chemical agent** [substance] with the phenotypic response of the second cell line to the **chemical agent** [substance].

43. A method of determining whether a **chemical agent** [substance] **that directly interacts with an enzyme** is an inhibitor or activator of **that enzyme** [a protein] which comprises:

(a) providing a **mammalian** test cell which overproduces a selected **enzyme** [protein] relative to a control cell which produces said **enzyme** [protein] at a lower level or essentially does not produce the **enzyme** [protein], and wherein production of said **enzyme** [protein] in said test cell evokes a responsive change in a phenotypic characteristic **of said test cell**, other than the level of said **enzyme** [protein] in said **test** cell per se, which is comparatively greater than in said control cell;

(b) treating said test cell containing the overproduced selected **enzyme** [protein] with said **chemical agent** [substance]; and

(c) examining the treated test cell to determine whether it exhibits a change in said phenotypic characteristic in response to said **chemical agent** [substance].

52. A method of determining whether a **chemical agent** [substance] **that directly interacts with a protein** is an inhibitor or activator of that protein which comprises:

(a) providing a **mammalian** test cell which overproduces a selected protein relative to a control cell which produces said protein at a lower level or essentially does not produce the protein, and wherein production of said protein in said test cell evokes a responsive change in a phenotypic characteristic **of said test cell**, other than the level of said protein in said **test** cell per se, which is comparatively greater than in said control cell;

(b) treating said test cell containing the overproduced selected protein with said **chemical agent** [substance], **wherein said chemical agent is suspected of being an inhibitor or activator of the biological activity of said protein**; and

(c) examining the treated test cell to determine whether it exhibits a change in said phenotypic characteristic in response to said **chemical agent** [substance].

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

INFORMATION DISCLOSURE STATEMENT		Docket Number: 395/35	
Application Number 09/510,562	Filing Date February 22, 2000	Examiner D. Saunders	Art Unit 1643
Invention Title METHOD OF SCREENING FOR PROTEIN INHIBITORS AND ACTIVATORS		Inventor(s) Gerard M. HOUSEY	

Address to:
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Washington D.C. 20231

1. In accordance with the duty of disclosure under 37 C.F.R. § 1.56 and in conformance with the procedures of 37 C.F.R. §§ 1.97(c) and 1.98 and M.P.E.P. § 609, Applicant hereby brings the references listed on the attached modified PTO Form No. 1449 to the attention of the Examiner. It is respectfully requested that the references be expressly considered during the prosecution of this application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

2. In accordance with 37 CFR § 1.98(d), copies of the references listed on the attached PTO Form 1449 which have been submitted in prior applications which are herein relied upon for an earlier filing date under 35 U.S.C. § 120 are not being resubmitted, but will be provided on request. A copy of each patent, publication or other information listed on the attached modified PTO Form 1449 which has not previously been submitted to the Patent Office in the prior applications is enclosed.

3. The following enclosed references (also listed on the PTO Form 1449) were cited by an opponent in the EPO Opposition Proceedings, or by an Examiner or by third parties during prosecution in the Japanese Patent Office:
   (1) Jetten, A.M., et al., (1986) Mol. Cell. Biol. 6:3341-3348.
   (2) Alberts, T. (1994) Molecular Biology of the Cell, 3rd ed., p. 1072.
   (3) Japanese Unexamined Patent Publication No. 1-500964 [provided herewith as WO 88/03168 which is the English language equivalent].
   (4) EP 327 369 A2
   (5) Fukuda, K., et al., (1987) Nature 327:623-625.
   (6) Takahashi, T., et al. (1985) J. Physiol. (Paris) 80:229-232.

4. In the parent application U.S. Ser No. 08/817,444, Applicant disclosed certain documents from the Opposition to EP 0 403 506 B1, which is the corresponding EP patent of this application. Applicant further provides copies and English translations of the following documents:
   (1) Patentee's response of October 8, 1999 to communication according to Rule 71(a) EPC issued by the European Patent Office.

(2) Brief in Opposition to EP 0 403 506 B1 filed in the European Patent Office by Hoechst AG (O1), October 7, 1999.
(3) English Translation of Brief in Opposition to EP 0 403 506 B1 filed in the European Patent Office by Hoechst AG (O1), October 7, 1999.
(4) Brief in Opposition to EP 0 403 506 B1 filed in the European Patent Office by Roche Diagnostics GmbH (O2), October 7, 1999.
(5) English Translation of Brief in Opposition to EP 0 403 506 B1 filed in the European Patent Office by Roche Diagnostics GmbH (O2), October 7, 1999.
(6) Brief in Opposition to EP 0 403 506 B1 filed in the European Patent Office by Boehringer Ingelheim GmbH (O3), November 15, 1999.
(7) English Translation of Brief in Opposition to EP 0 403 506 B1 filed in the European Patent Office by Boehringer Ingelheim GmbH (O3), November 15, 1999.
(8) Interlocutory Decision and marked copy of the disclosure and claims of EP 0 403 506 B1.

5. Pursuant to Interference No. 104,347, Applicant further includes:
(1) Berman Preliminary Motion (3) with Appendices A-C and the accompanying Third Declaration of Anthony B. Chen, Ph.D. (Exhibit 2032).
(2) Housey Opposition to Berman Preliminary Motion (3) with Appendices A and B and the accompanying First Declaration of James D. Griffin, M.D. (Exhibit 1010).
(3) Berman Reply to Housey Opposition with Appendices 1-5 and accompanying Fourth Declaration of Anthony B. Chen, Ph.D. (Exhibit 2037).

6. Two U.S. Patent publication are provided herewith. They are: U.S. Patent 5,877,007 to Housey, which issued from U.S. Application Ser. No. 08/473,169 and which is not relied upon for an earlier filing date under 35 U.S.C. § 120; and U.S. Patent 4,981,790 to Haseltine et al., which is of record in the aforementioned application.

7. As a first office action on the merits has not been mailed in this application, no fee is believed due. However, should any such fees be due, the Commissioner is authorized to charge Deposit Account No. 11-0600 for such fees. A duplicate copy of this communication is enclosed.

Dated: July 11, 2000

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